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THE AETIOLOGY OF HAEMOGLOBINURIC FEVER

W.E. Deeks

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Summarized by Prof. Yorke.

The Ætiology of Hæmoglobinuric Fever.

BY

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THE ÆTIOLOGY OF HÆMOGLOBINURIC FEVER.

By W. E. Deeks, M.D.

General Manager, Medical Department, United Fruit Co., New York.

THERE are few problems in tropical medicine which have caused more controversy than the ætiology of blackwater fever. Three theories have been advanced in explanation:

(1) That it is a symptom complex of a malarial infection.

(2) That it is caused by a specific organism which occurs in localities where malaria is prevalent.

(3) That the administration of quinine alone is responsible for precipitating an attack.

An enormous amount of literature and statistical data has accumulated on the subject. Most authorities now believe that blackwater fever is associated in some way with a malaria infection and that *Plasmodium falciparum* is chiefly, if not altogether, incriminated. If this hypothesis be correct the question naturally arises as to how hæmolysis occurs in a malaria infection. That it does not always follow an æstivo-autumnal infection, but only in a small percentage of these cases, is a self-evident fact to all practical workers in tropical climates where malaria is prevalent.

Certain facts in regard to its incidence appear to be fairly well established.

It is generally met with in malaria-infected individuals suffering from malnutrition, chronic organic disease, or some complicating infection which lowers resistance. It may develop in a few hours after unusual exposure to the hot sun, a severe chilling of the

surface of the body, over-exertion, fatigue, mental excitement or depression—in fact, anything that tends, temporarily or permanently, to lower the resistance of the patient.

Again, it frequently develops after the administration of a dose of quinine.

Any satisfactory hypothesis as to its ætiology must, therefore, be sufficiently comprehensive to explain all these factors.

In 1898 Bordet discovered that defribrinated rabbit's blood when injected at intervals of a few days into the peritoneal sac of a guinea-pig did not materially influence its activity, but in the body fluids or blood plasma of the guinea-pig a substance developed which rendered the plasma or sera capable of dissolving rabbit red blood cells, which power it did not previously possess. In other words, a hæmolytic agent or property was developed by the guinea-pig specific for rabbit blood cells, but for no other animal. This hæmolysin when injected into the rabbit in small doses caused hæmolysis of some of its red cells and in larger doses a sufficient number of red cells were hæmolysed to prove fatal. If, however, small doses were injected at intervals of a few days the rabbit developed in its plasma an *antihæmolytic* agent which prevented further damage. It is further interesting to note that these newly-developed agents or immune bodies are specific in each instance for the cell or antigen involved. Moreover, the same phenomenon could be observed when other than cells were injected into an alien animal. In each instance cytolytic substances were formed specific for all the cells injected.

These observations form a basis for the consideration of the development of the hæmolytic agent of hæmoglobinuric fever.

The malaria parasite must be considered to be an animal organism. It is unicellular and undifferentiated,

but has all the necessary functions of a parasitic animal. The protoplasmic cellular constituents associated with its vital functions are similar to those of higher animals. The organism is sensitive to temperature and other mechanical and chemical irritants; it eats, digests, grows, excretes, and reproduces itself—physiological properties possessed by all more highly specialized and organized multicellular organisms. If there be any difference in its protoplasmic activity we have no means — chemical or microscopical — of determining it. Fundamentally its structure and physiological activity is similar to that of more highly organized life. We have every reason, therefore, to believe that the hæmoglobin of the red cells, consumed by it during feeding, will develop hæmolytic agents in its body substance similar to those which are developed in the guinea-pig's blood, when the red cells of the rabbits are absorbed by it after injection. In other words, it can be logically inferred that each malaria parasite develops a hæmolytic property. In a malaria infection not only are red cells destroyed, but the colour index of the remaining individual red cells is lowered to a considerable degree. Is it not reasonable to believe that the resulting anæmia of a malaria-infected individual is due to this hæmolytic agent?

Furthermore, can we not correlate this action with that of the hookworm, which is a blood feeder, and which produces anæmia in the host? The small amount of blood which several hundred hookworms will destroy daily will not account for the severe anæmia observed in these cases — and it is now generally recognized that hookworms produce a hæmolytic agent, which is largely responsible for the resulting anæmia.

It would seem at first sight that very little hæmolysin could be produced by a malarial organism, but we know that in a severe malaria infection 20 per

cent. or more of the red cells may be invaded by parasites. This is equivalent to about 1,000,000 parasites to the cubic millimetre and 1,000,000,000 to the cubic centimetre, 30,000,000,000 to the oz., 480,000,000,000 to the lb., and in a man weighing 150 lb. there are about 12½ pints of blood, so that there would be about 6,000,000,000,000 parasites present in a severe malarial infection. Each red blood cell has a cubic capacity of approximately 1/171,277,000,000 of a cubic in., and according to J. G. Thomson at schizogony the *P. falciparum* occupies two-thirds of this space; its cubic capacity therefore is two-thirds of this, or 1/256,915,500,000 of a cubic in. This, multiplied by the number of parasites in a severe malaria infection, gives approximately 23·3 cubic in. of malarial protoplasmic material in a man weighing 150 lb. when 20 per cent. of his red blood cells are invaded.

We are all familiar with the anæmia and cachexia developed by a malignant tumour of similar cubic capacity. The malarial parasites also show a malignant action in their clinical symptomatology. The effect of 23·3 cubic in. of malarial material undoubtedly would be capable therefore of producing an enormous amount of hæmolysin in the human blood and, in response to its action, a large amount of antihæmolytic substance. As antihæmolysin undoubtedly is the result of the reaction of hæmolysin on the tissue cells, when a man is in good physical condition he is better able to develop antihæmolytic agents. Any of the depressing agencies which are considered as ætiological factors—chronic or acute—therefore, which interfere with the development of antihæmolytic bodies—a process more or less continuous in the presence of a malarial-infected individual—would permit extensive hæmolysis to ensue in such quantities that the liver and spleen would be unable to take care of the liberated hæmoglobin, and

hæmoglobinæmia would result, followed by a hæmoglobinuria.

In paroxysmal hæmoglobinurias following the administration of quinine, which destroys the trophozoites in large numbers, we have a condition in which large quantities of hæmolysin are suddenly liberated which the antihæmolytic bodies are unable to neutralize as fast as it is produced, and there is a consequent hæmoglobinæmia which overflows in the kidneys, producing hæmoglobinuria.

If this hypothesis be true it gives a reasonable explanation as to why in the treatment of post-hæmoglobinuric fever small doses of quinine should be given first, so as not to destroy too many parasites at once, and thus precipitate another attack. This is very necessary, as observed by clinical experience.

The confirmation of this theory of the causation of hæmoglobinuria rests on the ability to demonstrate the presence of hæmolysis in the blood immediately before the development of an attack of hæmoglobinuria, as its presence in the blood previous to this would be largely neutralized by anti-hæmolysis.

In this connection, the following quotation from J. G. Thomson's comprehensive monograph on "Researches on Blackwater Fever in Southern Rhodesia" is suggestive :—

"Successful cultures were obtained of the asexual cycle of eighteen cases of *P. falciparum,* and on five occasions in which no development took place I noted hæmolysis. There was no bacterial contamination, but it was observed that if the blood was drawn at a period corresponding to schizogony in the body hæmolysis invariably took place in the tubes. Simpson (1912), while working with malaria, also found evidence of hæmolysis during schizogony. Dr. Orpen tested several of the cultures by adding complement to the tubes after schizogony had taken place, and obtained some evidence that again a hæmolysin was present at this stage. This hæmolysis did not occur in controls. As, however, the numbers examined were very few, and chance

results are apt to occur, we did not feel justified in being positive about these results.

"We suggest, however, that by cultural methods and the use of careful technique and controls it may be possible to demonstrate hæmolysins present at certain stages of the asexual cycle, e.g., during complete schizogony. Miss Trutter kindly examined the blood groups of a number of blackwater fever cases, but here we were unable to state that the disease showed any preference for one of these. It is probable that a hæmolysin can be demonstrated only at certain periods of the asexual cycle. The chances of detecting it may rapidly vanish as the disease progresses. We were quite unable to detect any hæmolysin in the serum of blackwater fever at any period of the disease, but, as we have pointed out, this by no means proves that a serum hæmolysin is not present."

Confirmation of the observation of Dr. Thomson and others on the presence of hæmolysin at the time of schizogony would support the theory suggested on the ætiology of blackwater fever.

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